Research Article

Formulation Design and Optimization of Novel Fast Disintegrating Tablets of Atenolol Using Super Disintegrants

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ABSTRACT

The demand for fast disintegrating tablets has been growing, during the last decade especially for geriatric and pediatric patients because of swallowing difficulties. Atenolol a selective β – Adrenergic Blocker is widely used to reduce elevated blood pressure in hypertensive patients. Fast disintegrating tablets of Atenolol were prepared by superdisintegrant addition method. The tablets were prepared by direct compression method using super disintegrants like crospovidone, croscarmellose, sodium starch glycolate. The blend was examined for various pre compression parameters. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio, *in vitro* dispersion time and *in vitro* drug release pattern (in pH 6.8 phosphate buffer). Among all the formulations, the formulation prepared by using 8% w/w of croscarmellose (ACC5) emerged as the overall best formulation, based on the *in vitro* dispersion time, wetting time, water absorption ratio and *in-vitro* dissolution profile compared to control tablet formulation. Short-term stability studies on the formulations indicated that there are no significant changes in drug content and *in vitro* dispersion time.

Keywords: Atenolol, Croscarmellose, Crospovidone, Direct compression method, Fast disintegrating tablet, Sodium starch glycolate.

INTRODUCTION

Oral routes of drug administration have wide acceptance up to 50 – 60% of total dosage forms. This is perhaps the most appealing route for the delivery of drugs. Of the various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, self medication, pain avoidance, stability compared with oral liquids, and moreover it is more tamperproof than capsules.[1-4] One important drawback of this solid dosage forms for some patients, is the difficulty to swallow such as pediatric and geriatric patients. Swallowing problem is common in children because of their underdeveloped muscular and nervous systems. In some cases like motion sickness, sudden episodes of allergic attack or coughing, and during unavailability of water, swallowing conventional tablets is difficult. To fulfill these medical needs, formulators have devoted considerable efforts for developing a novel type of dosage form for oral administration known as orally disintegrating tablets (MDT).[5, 6]

Innovators and inventor companies have given these tablets various names such as orally disintegrating tablets (ODT), mouth dissolving (MD), fast melting, fast dissolving or orodisperse tablets. The European Pharmacopoeia defines orodisperse as a tablet that can be placed in the mouth where it disperses rapidly before swallowing. These dosage forms dissolve or disintegrate in the oral cavity within seconds without the need of water or chewing. The bioavailability of drug is dependent on in vivo disintegration, dissolution, and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets. The task of developing rapidly disintegrating tablets is accomplished by using a suitable diluents and superdisintegrants.[7]

Researchers have formulated ODT for various categories of drugs, which are used for therapy in which rapid peak plasma concentration is required to achieve desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, anti-allergic and drugs for erectile dysfunction.[8] Atenolol is a Beta – Adrenergic blocking drug coming under the classification of cardiovascular agents that reduce elevated blood pressure in hypertensive patients. These agents do have some central effect on catecholaminergic neurons.[9]

The concept of formulating fast disintegrating tablets containing Atenolol offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability. The objective of this study was to enhance the safety and efficacy of drug molecule, achieve the better compliance, solve the problem of difficulty of swallowing, enhance onset of action, and provide stable dosage form. Mouth dissolving tablets of Atenolol were formulated by direct compression method using various superdisintegrants.

MATERIALS AND METHODS

Atenolol was obtained as a gift sample from Aurabindo labs, crospovidone, croscarmellose, sodium starch glycolate and Micro crystalline cellulose were from S.D. fine chemicals and all other chemicals used were of analytical grade.

Analytical method for estimation of the Atenolol drug (UV method)

In the present investigation, Atenolol was estimated by UV/VIS spectrophotometry in 0.1N HCl. The *in vitro* dissolution study was also carried out in 0.1N HCl (pH 1.2).

Preparation of stock solution

Atenolol (100mg) was accurately weighed and transferred into the 100 ml amber colored volumetric flask. It was dissolved in 0.1N HCl and volume was made up to the mark with 0.1N HCl to get a 1000 µg/ml solution. From this 10 ml was pipette out and then diluted up to 100 ml with 0.1N HCl. From that solution again 10 ml pipetted out and diluted up to 100 ml in amber colored volumetric flask with 0.1N HCl to get a stock solution of 10µg/ml.

UV absorption maxima of Atenolol

UV scanning was done for 10µg/ml drug solution from 200-400 nm in 0.1N HCl as a blank using Shimadzu double beam UV/VIS spectrophotometer. The wavelength maximum was found to be at 225 n.

Preparation of standard curve

From the stock solution 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml were transferred to 10 ml amber colored volumetric flasks and diluted with the 0.1N HCl, up to the mark to obtain Atenolol concentration of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 µg/ml respectively. Absorbance of each solution was measured at 225 nm.

Preparation of fast disintegrating tablets of Atenolol[10, 11]

Fast disintegrating tablets of Atenolol were prepared by direct compression according to the formulae given in Table 1. All the ingredients were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order. The powder blend is then lubricated with magnesium stearate [1%w/w] and talc [1%w/w], and this lubricated blend was compressed into tablets of 200 mg using 8 mm flat face round tooling on a single punch tablet machine. A batch of 60 tablets was prepared for all the designed formulations. The formulation designs have been shown in (Table 1).

Evaluation of Powder Blend

All micrometric properties of powder blend like angle of repose, Tapped density, Bulk density, Carr's index, Hausner ratio, porosity were determined. The results are depicted in (Table 2).

Evaluation of fast disintegrating tablets of Atenolol

Tablet Hardness [12]

The hardness of the tablet was determined using Monsanto Hardness Tester, a tablet hardness of 2-4 kg/cm^2 is considered adequate. Averages of three determinations have been taken.

Weight Variation Test [12]

Twenty tablets were selected at random and weighed individually on shimadzu BL-220. The individual weights were compared with the average weight for determination of weight variation.

Friability [12]

Friability of the tablets was determined by using Roche friabilator. Tablets of a known weight (20 tablets) are kept in the drum for a fixed time (100 rpm) and weighed again. Percentage friability was calculated from the loss in weight. The weight loss should not be more than 1%. Averages of three determinations have been taken.

Tablet Thickness [12]

Tablet thickness was measured using vernier calliper. The thickness was measured by placing tablet between two arms of the vernier callipers. Averages of three determinations have been taken.

Drug Content Uniformity [13]

Twenty tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 20mg of Atenolol was transferred into a 100ml standard flask and volume was made up with a 6.8 pH buffer. Further 1ml of the above solution was diluted 10 ml with 6.8 pH buffer and absorbance of the resulting solution was observed at 275 nm. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

In-vitro Dispersion Time [14]

For determination of *in-vitro* dispersion time, one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5ºC and the time required for complete dispersion was determined. Averages of three determinations have been taken.

Wetting Time and Water Absorption Ratio (R) [15]

Twice folded tissue paper was placed in a Petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation: $R = 100 \times (wa - wb)/ wb$

Where wb and wa were tablet weights before and after water absorption, respectively.

***In-vitro* Dissolution study** [16]

In-vitro dissolution of Atenolol orodispersible tablet was studied in USP XXIII type-II dissolution apparatus (Electrolab, Model-TDT 06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5ºC as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium (5 ml) were

withdrawn at specified intervals of time, filtered through Whatman filter paper and analyzed spectrophotometrically for drug content by measuring the absorbance at 275 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of Atenolol released was calculated and plotted against time.

Stability Testing

Short-term stability studies on the promising formulation (ACC5) were carried out by storing the tablets (in amber colored rubber stoppered vials) at 40°/ 75% Relative humidity over a period 3 months. At interval of one month, the tablets were visually examined for any physical changes, changes in drug content and *in-vitro* dispersion time.

Table 1: Formulation design of Atenolol fast disintegrating tablet

Ingredients (mg)	ACP1	ACC2	ASS3	ACP4	ACC5	ASS6	AC7
Drug	25	25	25	25	25	25	25
Crospovidone	4	-------	-----	8	------	------	-----
Croscarmellose	-----	4	-----	------	8	------	------
Sodium starch glycolate	------	------	4	------	-----	8	------
Mannitol	145	145	145	141	141	141	149
Microcrystalline cellulose	20	20	20	20	20	20	20
Magnesium stearate	1	1	1	1	1	1	1
Vanillin	3	3	3	3	3	3	3
Saccharin sodium	2	2	2	2	2	2	2
Total (mg)	200	200	200	200	200	200	200

Table 2: Pre compression parameters of Atenolol fast disintegrating tablet

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (^{o})
ACP1	0.351	0.414	15.21	1.1794	28^o 07'
ACC2	0.386	0.428	9.81	1.1088	29^o 02'
ASS3	0.397	0.411	5.2	1.035	28^o 03'
ACP4	0.405	0.426	5.0	1.0518	27^o 08'
ACC5	0.397	0.441	9.9	1.1108	28^o 07'
ASS6	0.378	0.428	11.68	1.1322	29^o 09'
AC7	0.376	0.436	13.76	1.1595	27^o 01'

Table 3: Evaluation of Physical Parameters of fast disintegrating tablets of Atenolol

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%w/w)	*In- vitro* dispersion time (secs)	Wetting time (secs)	Water absorption ratio (secs)	Drug Content (%)
ACP1	5.20±0.32	3.5±0.40	0.80	27.45±1.23	29.76±0.78	65.34±1.22	98.3±0.34
ACC2	5.18±0.17	4±0.34	0.35	33.32±0.80	35.66±1.23	77.56±1.34	96±0.67
ASS3	5.17±0.28	3.5±0.54	0.65	23.54±2.19	26.34±2.34	59.89±2.01	97.09±1.22
ACP4	5.25±0.37	4±0.09	0.50	45.76±1.67	46.65±2.23	84.34±0.98	98±0.78
ACC5	5.30±0.13	4±1.43	0.75	16.28±2.56	17.45±1.45	90.23±0.78	98.8±0.66
ASS6	5.30±0.17	4.5±0.23	0.80	19.50±1.34	21.86±0.89	74.78±1.22	97.2±0.69
AC7	5.20±0.21	4±1.23	0.60	307.32±2.15	310.23±0.88	67.56±2.10	97.5±0.45

RESULTS AND DISCUSSION

Fast disintegrating tablets of Atenolol were prepared by direct compression method employing crospovidone, croscarmellose sodium and sodium starch glycolate as super-disintegrants in different ratios with microcrystalline cellulose. Directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance mouth feel and aspartame which serves as a sweetening agent and helps in masking slight bitter taste of the drug. A total of seven formulations and a control formulation (AC7) (without super-disintegrant) were designed. As the blends were free flowing (angle of repose <30°, and Carr's index <15%) tablets obtained were of uniform weight (due to

uniform die fill), with acceptable variation as per IP specification i.e., below 7.5%.

Thickness ranged from 5.17mm -5.20mm. Uniformity of weight is observed within the IP limit. The max % deviation allowed is ±7.5% for tablets of 200 mg, all the tablets complies with the official limit. Hardness was observed to within the range of 3.5-4.5 Kg/cm^2, this hardness is considered optimum for uncoated tablets, according to the stability factor. Friability was observed between 0.3-0.8%w/w. It should not be more than 1% w/w, this is the recommended limit and all the tablets are found to be within the limit. Drug content was found to be in the range of 96 to 100%, which is within acceptable limits. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 50-85% and 12-56 s respectively. The results are shown in (Table 3). *In vitro* dissolution studies for all the formulations were carried out in pH 6.8 phosphate buffer, and the various dissolution profiles are depicted in (Table 4) and (Figure 1).

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of ACC5 showed all the characteristic peaks of Atenolol pure drug, thus confirming that no interaction of drug occurred with the components of the formulation.

Table 4: Comparison of percentage drug release of fast disintegrating tablets of Atenolol

Formulation	Ratio (w/w)	Super disintegrants	*In vitro* release in 60min (%)
ACP1	2%	Cros povidone	86.21
ACC2	2%	Cros carmellose	85.17
ASS3	2%	Sodium starch glycolate	82.12
ACP4	4%	Cros povidone	92.05
ACC5	4%	Cros carmellose	98.67
ASS6	4%	Sodium starch glycolate	89.46
AC7	-----	Without super disitegrantes	68.48

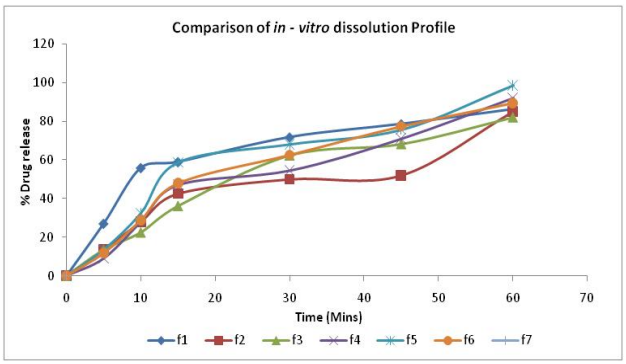

Figure 1: Comparison of in-*vitro* dissolution profile of Atenolol fast disintegrating tablets.

Table 5: Accelerated stability studies of fast disintegrating tablets of Atenolol ACC5

Temperature (^{0}C)	Relative humidity (%)	Time (days)	Thickness (mm)	Hardness (kg/cm^2)	Drug content (%)	*In-vitro* dispersion time (secs)	In-vitro drug release (%)
45±2	75±2	0	5.11	3.95	98.0	16	98.67
45±2	75±2	15	5.11	3.95	98.0	17	98.64
45±2	75±2	45	5.12	3.94	97.7	18	98.14

Selection of optimized Atenolol fast disintegrating tablet on its comparison with control tablet

The selection of the optimized formulation depends on, *in vitro* dispersion time, wetting time, water absorption ratio and in-vitro dissolution profile. To develop effective fast dissolving formulation, it is important to determine all the above parameters. Overall, the formulation ACC5 was found to be promising and has shown, *in vitro* dispersion time of 16 s, wetting time of 12 s and water absorption ratio of 85%, fast dissolution profile of 98.67% within 60 minutes when compared to control formulation (AC7) which shows 244 s, 255 s and 50% values respectively for the above parameters (Table 2). So considering all the parameters related to the fast disintegrating formulation, batch ACC5 containing croscarmellose as superdisintegrant was found to be the optimized batch among all other batches.

Short term accelerated stability studies were conducted for formulation ACC5 and the result observed reveals that there was no significant difference in the evaluation parameters namely thickness, hardness, drug content, *in-vitro* dispersion time & % drug release. This inference shows that the formulation ACC5 would be stable, for long time storage (Table 5).

CONCLUSION

The present study conclusively indicates that the formulation ACC5 (croscarmellose 4% as a superdisintegrant) is very much promising as fast disintegrating tablets of Atenolol with an *in vitro* dispersion time of 16 secs, wetting time of 12 secs and water absorption ratio of 85% and in-vitro fast dissolution profile of 98.67% within 60 minutes.

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